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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/147,919	03/23/1999	MARY JANE CARDOSA	20239-703	2431

7590 08/27/2003

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EXAMINER
MOSHER, MARY

ART UNIT	PAPER NUMBER
1648	12

DATE MAILED: 08/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/147,919	Applicant(s) Cardosa et al
	Examiner Mosher	Art Unit 1648

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *1/7/2003, 4/8/2003* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *15-28 and 32-38* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☒ Claim(s) *27, 28, and 32* is/are allowed.

6) ☒ Claim(s) *15-26 and 33-38* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Prosecution Application

The request filed on January 7, 2003 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/147,919 is acceptable and a CPA has been established. Since the requested suspension period of three months has passed, an action on the CPA follows.

Specification

The disclosure is objected to because of the following informalities: On page 11, the specification refers to drawings which were not part of the application as filed.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claims 15-26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. On consideration, the specification does not in any way provide blazemarks to the general concept of an MVA vector with homologous Dengue antigen inserts. The specification throughout discusses "antigens from all four dengue virus serotypes...wherein the dengue virus antigens is selected from preM, E, and/or NS1 antigen" (e.g. specification page 6; original claims 2-3). However, the Markush group of "antigens from all four serotypes...selected from preM, E, and/or NS1" does include obvious species of 4 preM antigens,

4 E antigens, or 4 NS1 antigens. Therefore, claims 15-26 are rejected as involving new matter, but claims 33-38 are not.

In the response filed April 8, 2003, applicants point to the word "homologous" on specification page 8. The word does appear there, but in the context of using homologous recombination between MVA sequences to insert foreign nucleotide sequences. This context does not in any way suggest inserting dengue sequences which are homologous to each other.

To quote Robert L. Harmon, "entitlement to a filing date does not extend to subject matter that is not disclosed but would be obvious over what is expressly disclosed....In particular, it is not sufficient for purposes of the written description requirement that the disclosure, when combined with knowledge in the art, would lead one to speculate as to modifications that the inventor might have envisioned but failed to disclose." (R.L. Harmon, Patents and the Federal Circuit, Fifth edition, BNA books, 2001; pages 232-233).

Claims 15-26, 33-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. These claims have been amended to require that the MVA include 2-4 sequences encoding the same Dengue antigen from 2-4 serotypes. Applicant's response points out that recombination between homologous sequences in poxvirus vectors is a recognized problem in the art. The specification provides no teachings of how to avoid or overcome this problem, and provides no working examples of the invention as now claimed. Since this appears to be a

recognized problem in the art, and the specification does not teach how to overcome this problem, it is concluded that undue experimentation would be required to make and use the claimed poxvirus with more than one homologous insert of Dengue antigens.

The declaration filed by Dr. Leyrer has been considered. It is noted that the declaration refers to appendixes A - D, but no appendixes were provided. In the declaration, Dr. Leyrer provides evidence that an MVA recombinant with homologous PrM sequences from types 1, 2, 3, and 4 was successfully constructed, and was found to be stable. It is noted that the construction used four different insertion sites (deletions 1, 2, 4, and intergenic region). The specification does not teach one to choose different insertion sites for each of the dengue genes, and does not teach deletion 1, deletion 4, or intergenic region as insertion sites. The specification points to only two insertion sites, deletion II or III, see page 8, second full paragraph, and provides detailed teachings for only one site, deletion II, see Examples 4-8. It is further noted that the successful construction used spontaneous recombination between two different MVA constructs under unspecified "selective conditions" to obtain the 4-serotype virus. This procedure is nowhere disclosed in the specification. In conclusion, the examiner is convinced (despite the absence of the supporting data) that it is possible to obtain a reasonably stable MVA containing 4 different homologs of a dengue gene, but the construction of this virus involved materials and procedures that go well beyond the disclosure in the specification.

Furthermore, applicant argues that "immunization against more than one Dengue virus serotype using a single antigen was thought to be dangerous due to immune and/or antibody

enhancement." If this was a concern to one skilled in the art, then that skilled artisan would not unquestioningly accept assertions that the claimed products can be successfully used to immunize against all four Dengue serotypes. The specification does not teach how to alleviate immune or antibody enhancement should such enhancement occur using the tetravalent, single-subunit vaccine, or provide any evidence that the dangerous enhancement does not occur. Considering the state of the art, as applicant has characterized it, the limited teachings in the specification, and the absence of working examples, it is concluded that undue experimentation would be required to use the pharmaceutical compositions and methods as claimed in claims 20-26.

Claim Rejections - 35 USC § 103

Claims 15-26, 33-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paoletti et al (5744141 or 5514375) in view of [Sutter (C2) or Altenburger (5185146)] and [Monath et al or Kelly et al (6074865)] and [Paoletti (WO92/15672) or Boursnell WO 92/16636]. As discussed previously, the US patents of Paoletti teach a recombinant vaccinia virus comprising the entire preM, E, and NS-1 dengue coding sequence, see Example 13 in each patent. This differs from the claimed invention in two respects: Paoletti teaches an insert from one serotype, not two or more inserts from different serotypes, and Paoletti teaches a vaccinia vector which is not MVA. As discussed in previous actions, Sutter and Altenburger disclose advantages of using MVA as a vaccine vector in place of other vaccinia strains, Monath and Kelly both suggest tetravalent vaccines to simultaneously vaccinate against all four Dengue serotypes. Paoletti WO92/15672 provides a working example of a trivalent poxvirus construct, where three

homologous genes of different serotypes are placed in a single poxvirus vector. Applicant argues that the genes in Paoletti are not homologous because they are avian influenza hemagggglutinin genes and can vary in base composition and length. This is not convincing, because one skilled in the art would consider all the avian influenza hemagglutinin genes as homologs, despite minor variations in length and variation in sequence. Boursnell explicitly teaches inserting plural homologous sequences in vaccinia, and teaches one solution to the recognized problem of recombination between homologous sequences, see pages 5-7. Furthermore, Boursnell also provides a working example where two sets of homologous genes (two genes each from two different serotypes) are placed in a single poxvirus vector. Therefore, it is concluded that it would have been within the ordinary skill of the art to produce an MVA recombinant expressing more than one homologous gene of plural dengue serotypes, for the purpose of obtaining simultaneous vaccination against plural serotypes as suggested by Monath and Kelly, with reasonable expectation of sucess in producing the multivalent recombinant consistant with sucess in analogous art by Paoletti WO 92/15672 and Bournell. It is maintained that the invention as a whole is prima facie obvious.

Applicant argues that one of skill in the art would not have had a reasonable expectation of success, because recombination of homologous sequences was a recognized problem, and because immunization against more than one serotype using a single antigen was thought to be dangerous due to immune and/or antibody enhancement. However, both Paoletti and Boursnell teach that constructs containing homologous sequences can be made successfully. Monath

suggests that dangerous enhancement is a concern for subunit protein vaccines (because the proteins induce only a humoral response, which can lead to antibody-dependent enhancement as the level of circulating antibody declines with time). Monath does not suggest the same concern for live, vectored vaccines (which are well known to induce robust responses by both humoral and cell-mediated immunity).

Allowable Subject Matter

Claims 27, 28, and 32 are allowed, for reasons of record in paper no. 9.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary E. Mosher, Ph.D. whose telephone number is (703) 308-2926. The examiner can normally be reached on Monday -Thursday and alternate Fridays from 6:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027. The fax phone numbers for this Group are now (703) 872-9306 for Before Final responses, and (703) 872-9307 for After Final responses. Faxes for this Group can also be sent to (708) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

August 22, 2003

MARY E. MOSHER
PRIMARY EXAMINER
GROUP ~~1800~~ 1601